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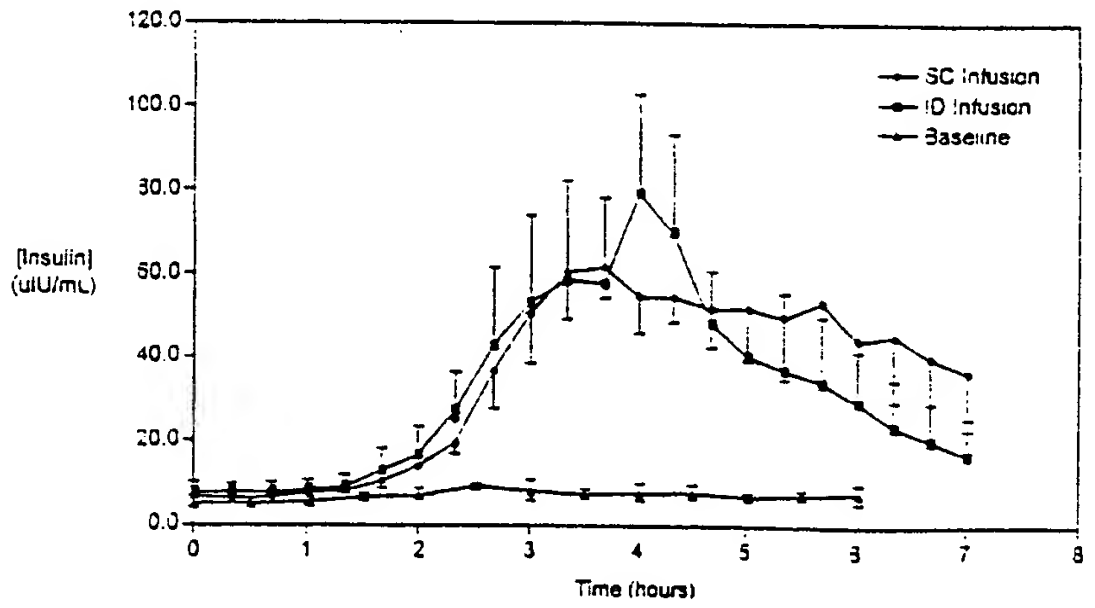
(54) Title: NEEDLE FOR INTRADERMAL DELIVERY OF SUBSTANCES HAVING PENETRATION LIMITING MEANS



(57) Abstract: The present invention provides improved methods for ID delivery of drugs and other substances to humans or animals. The methods employ small gauge needles, especially microneedles, placed in the intradermal space to deliver the substance to the intradermal space as a bolus or by infusion. It has been discovered that the placement of the needle outlet within the skin and the exposed height of the needle outlet are critical for efficacious delivery of active substances via small gauge needles to prevent leakage of the substance out of the skin and to improve absorption within the intradermal space. The pharmacokinetics of hormone drugs delivered according to the methods of the invention have been found to be very similar to the pharmacokinetics of conventional SC delivery, indicating that ID administration according to the methods of the invention is likely to produce a similar clinical result (i.e., similar efficacy) with the advantage of reduction or elimination of pain for the patient. Delivery devices which place the needle outlet at an appropriate depth in the intradermal space and control the volume and rate of fluid delivery provide accurate delivery of the substance to the desired location without leakage.

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NEEDLE FOR INTRADERMAL DELIVERY OF SUBSTANCES HAVING PENETRATION LIMITING MEANS

FIELD OF THE INVENTION

The present invention relates to methods and devices for administration of substances into the skin.

BACKGROUND OF THE INVENTION

Conventional needles have long been used to deliver drugs and other substances to humans and animals through the skin, and considerable effort has been made to achieve reproducible and efficacious delivery through the skin while reducing or eliminating the pain associated with conventional needles. Certain transdermal delivery systems eliminate needles entirely, and rely on chemical mediators or external driving forces such as iontophoretic currents or sonophoresis to breach the stratum corneum painlessly and deliver substances through the skin. However, such transdermal delivery systems are not sufficiently reproducible and give variable clinical results.

Mechanical breach of the stratum corneum is still believed to be the most reproducible method of administration of substances through the skin, and it provides the greatest degree of control and reliability. Intramuscular (IM) and subcutaneous (SC) injections are the most commonly used routes of administration. The dermis lies beneath the stratum corneum and epidermis, beginning at a depth of about 60-120 μm below the skin surface in humans, and is approximately 1-2 mm thick. However, intradermal (ID) injection is rarely used due to the difficulty of correct needle placement in the intradermal space, the difficulty of maintaining placement of the needle in the intradermal space, and a lack of information and knowledge of the pharmacokinetic profiles for many drugs delivered ID. In addition, little is known about fluid absorption limits in dermal tissue and the effect of depot time on drug stability. However, ID administration of drugs and other substances may have several advantages. The intradermal space is close to the capillary bed to allow for absorption and systemic distribution of the substance but is above the peripheral nerve net which may reduce or eliminate injection pain. In addition, there are more suitable and accessible ID

depth of penetration of the microneedles nor do they report any results suggesting a clinically useful glucose response using this method of administration. Further, there is no evidence of accurate or reproducible volume of delivery using such a device. WO 99/64580 suggests that substances may be delivered into skin via microneedles at clinically relevant rates. However, it fails to appreciate that clinical efficacy is dependent upon both accurate, quantitative, and reproducible delivery of a volume or mass of drug substance and the pharmacokinetic uptake and distribution of that substance from the dermal tissue.

SUMMARY OF THE INVENTION

The present invention improves the clinical utility of ID delivery of drugs and other substances to humans or animals. The methods employ small gauge needles, especially microneedles, placed in the intradermal space to deliver the substance to the intradermal space as a bolus or by infusion. It has been discovered that the placement of the needle outlet within the skin is critical for efficacious delivery of active substances via small gauge needles to prevent leakage of the substance out of the skin and to improve absorption within the intradermal space. ID infusion is a preferred method for delivery according to the invention because lower delivery pressures are required. This also reduces the amount of substance lost to the skin surface due to internal pressure which increases as fluid accumulates within the skin prior to absorption. That is, infusion minimizes effusion of the substance out of the tissue. Infusion also tends to reduce painful swelling and tissue distension and to reduce internal pressure as compared to the corresponding bolus dose. The pharmacokinetics of hormone drugs delivered according to the methods of the invention have been found to be very similar to the pharmacokinetics of conventional SC delivery of the drug, indicating that ID administration according to the methods of the invention is likely to produce a similar clinical result (i.e., similar efficacy) with the advantage of reduction or elimination of pain for the patient. Delivery devices which place the needle outlet at an appropriate depth in the intradermal space and control the volume and rate of fluid delivery provide accurate delivery of the substance to the desired location without leakage.

manually by the practitioner, with or without the assistance of indicator means to indicate when the desired depth is reached. Preferably, however, the device has structural means for limiting skin penetration to the depth of the intradermal space. Such structural means may include limiting the length of the needle or catheter available for penetration so that it is no longer than the depth of the intradermal space. This is most typically accomplished by means of a widened area or "hub" associated with the shaft of the needle, or for needle arrays may take the form of a backing structure or platform to which the needles are attached (see, for example, US Patent 5,879,326; WO 96/37155; WO 96/37256). Microneedles are particularly well suited for this purpose, as the length of the microneedle is easily varied during the fabrication process and microneedles are routinely produced in less than 1 mm lengths. Microneedles are also very sharp and of very small gauge (typically about 33 gauge or less) to further reduce pain and other sensation during the injection or infusion. They may be used in the invention as individual single-lumen microneedles or multiple microneedles may be assembled or fabricated in linear arrays or two-dimensional arrays to increase the rate of delivery or the amount of substance delivered in a given period of time. Microneedles may be incorporated into a variety of devices such as holders and housings which may also serve to limit the depth of penetration or into catheter sets. The devices of the invention may also incorporate reservoirs to contain the substance prior to delivery or pumps or other means for delivering the drug or other substance under pressure. Alternatively, the device housing the microneedles may be linked externally to such additional components.

It has been found that certain features of the intradermal administration protocol are essential for clinically useful pharmacokinetics and dose accuracy. First, it has been found that placement of the needle outlet within the skin significantly affects these parameters. The outlet of a smaller gauge needles with a bevel has a relatively large exposed height (the vertical "rise" of the outlet). Although the needle tip may be placed at the desired depth within the intradermal space, the large exposed height of the needle outlet allows the substance being delivered to be deposited at a much shallower depth nearer the skin surface. As a result, the substance tends to effuse out of the skin due to backpressure exerted by the skin itself and to pressure built up from accumulating fluid from the injection or infusion. For example, 200 μm microneedles are often cited as suitable

of the skin. The appropriate delivery rates and volumes to obtain these effects for a selected substance may be determined experimentally using only ordinary skill. That is, in general the size of the weal increases with increasing rate of delivery for infusion and increases with increasing volume for bolus injection. However, the size and number of microneedles and how closely together they are placed can be adjusted to maintain a desired delivery rate or delivery volume without adverse effects on the skin or the stability of the needle in the skin. For example, increasing the spacing between the needles of a microneedle array device or using smaller diameter needles reduces the pressure build-up from unabsorbed fluid in the skin. Such pressure causes weals and pushes the needle out of the skin. Small diameter and increased spacing between multiple needles also allows more rapid absorption at increased rates of delivery or for larger volumes. In addition, we have found that ID infusion or injection often provides higher plasma levels of drug than conventional SC administration, particularly for drugs which are susceptible to *in vivo* degradation or clearance. This may, in some cases, allow for smaller doses of the substance to be administered through microneedles via the ID route, further reducing concerns about blistering and backpressure.

The administration methods contemplated by the invention include both bolus and infusion delivery of drugs and other substances to human or animal subjects. A bolus dose is a single dose delivered in a single volume unit over a relatively brief time period, typically less than about 5-10 min. Infusion administration comprises administering a fluid at a selected rate (which may be constant or variable) over a relatively more extended time period, typically greater than about 5-10 min. To deliver a substance according to the invention, the needle is placed in the intradermal space and the substance is delivered through the lumen of the needle into the intradermal space where it can act locally or be absorbed by the bloodstream and distributed systemically. The needle may be connected to a reservoir containing the substance to be delivered. Delivery from the reservoir into the intradermal space may occur either passively (without application of external pressure to the substance to be delivered) or actively (with the application of pressure). Examples of preferred pressure-generating means include pumps, syringes, elastomeric membranes, osmotic pressure or Belleville springs or washers. See, for example, US Patent No. 5,957,895; US Patent No. 5,250,023; WO 96/17648; WO 98/11937; WO 99/03521. If desired, the rate of delivery of the

via the conventional SC route. The decrease in blood glucose response is also similar between the two. Although 9 U/hr. is a higher administration rate than is typically used medically, these results also demonstrate the ability of dermal tissues to readily absorb and distribute medicaments which are infused via this pathway.

A similar experiment was conducted using human parathyroid hormone 1-34 (PTH). PTH was infused for a 4 hr. period, followed by a 2 hr. clearance. Flow rates were controlled by a Harvard syringe pump. Control SC infusion was through a standard 31 gauge needle inserted into the SC space lateral to the skin using a "pinch-up" technique. ID infusion was through the bent 30 gauge needle described above. A 0.64 mg/mL PTH solution was infused at a rate of 75 μL/hr. Weight normalized PTH plasma levels are shown in Fig. 3. This data demonstrates the efficacy of this route of administration for additional hormone drugs, and indicates that ID infusion may actually provide higher plasma levels for drugs that are susceptible to *in vivo* biological degradation or clearance.

EXAMPLE 2

ID insulin delivery was demonstrated in swine using a hollow silicon microneedle connected to a standard catheter. The catheter was attached to a MiniMed 507 insulin pump for control of fluid delivery.

A hollow, single-lumen microneedle (2 mm total length and 200 X 100 μm OD, corresponding to about 33 gauge) with an outlet 1.0 μm from the tip (100 μm exposed height) was fabricated using processes known in the art (US Patent No. 5,928,207) and mated to a microbore catheter commonly used for insulin infusion (Disetronic). The distal end of the microneedle was placed into the plastic catheter and cemented in place with epoxy resin to form a depth-limiting hub. The needle outlet was positioned approximately 1 mm beyond the epoxy hub, thus limiting penetration of the needle outlet into the skin to approximately 1 mm., which corresponds to the depth of the intradermal space in swine. The patency of the fluid flow path was confirmed by visual observation, and no obstructions were observed at pressures generated by a standard 1 cc syringe.

WHAT IS CLAIMED IS:

1. A method for delivering a substance into skin comprising delivering the substance into an intradermal space within the skin through a small gauge needle inserted into the intradermal space, wherein an outlet of the needle is inserted at a depth within the skin such that leakage of the substance to the surface of the skin is substantially prevented.

2. The method of Claim 1 wherein the needle is selected from the group consisting of microneedles, catheter needles, and injection needles.

3. The method of Claim 1 wherein a single needle is inserted.

4. The method of Claim 1 wherein multiple needles are inserted.

5. The method of Claim 1 wherein the substance is a liquid delivered by pressure directly on the liquid.

6. The method of Claim 1 wherein a hormone is delivered.

7. The method of Claim 6 wherein the hormone is selected from the group consisting of insulin and PTH.

8. The method of Claim 1 wherein the substance is infused.

9. The method of Claim 1 wherein the substance is injected as a bolus.

10. The method of Claim 1 wherein the needle is about 300 μm to 2 mm long.

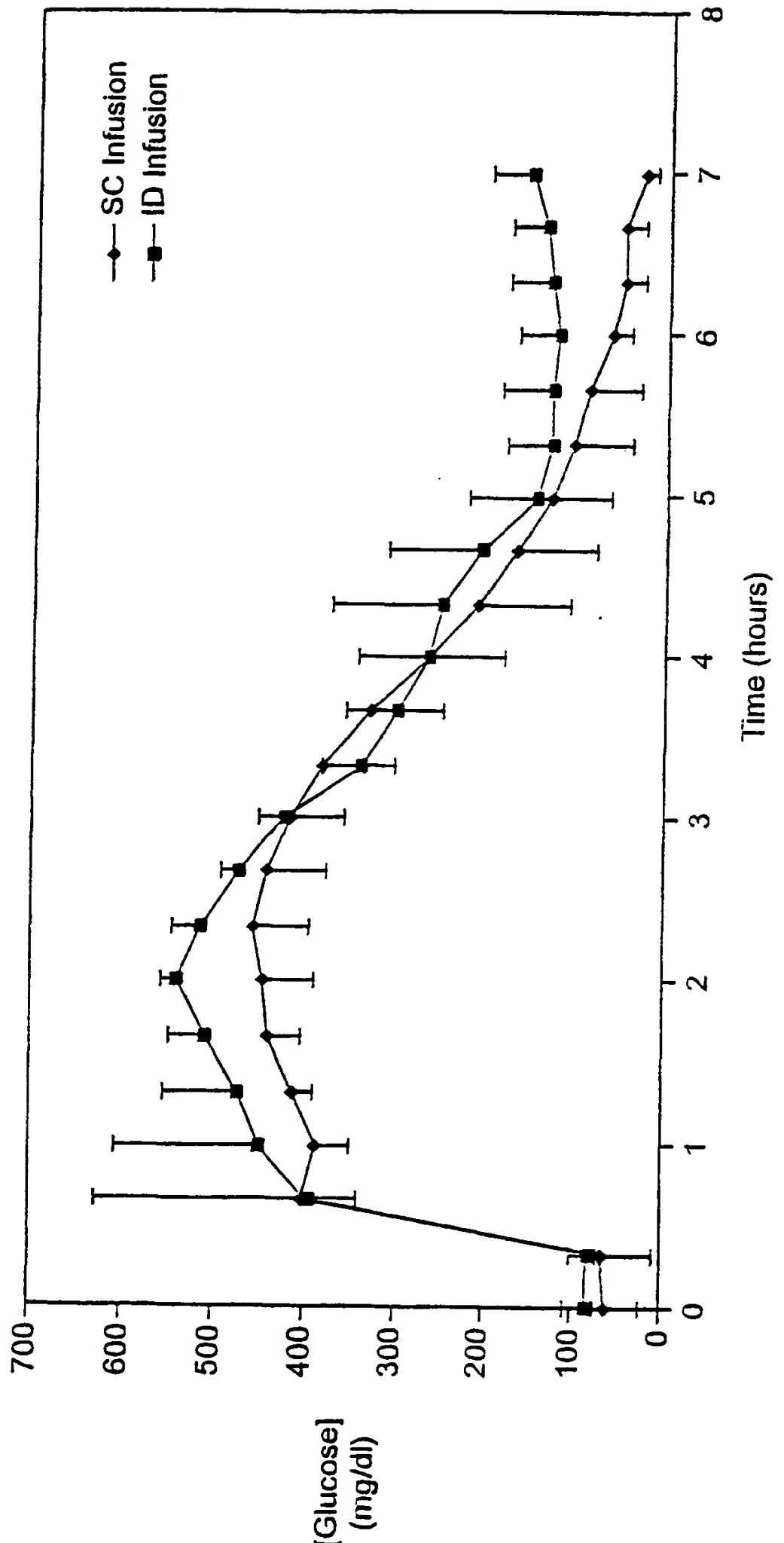
21. The needle of Claim 20 which is about 500 μm to 1 mm long.

22. The needle of Claim 17 which is contained in a device comprising a reservoir in fluid communication with the needle.

23. The needle of Claim 22 which is contained in a device further comprising pressure-generating means for delivering the substance through the needle.

24. The needle of Claim 23 wherein the pressure-generating means provides variable control of substance delivery rate.

FIG. 2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ID Infusion
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100
200
300
400
500
600
700
0
1
2
3
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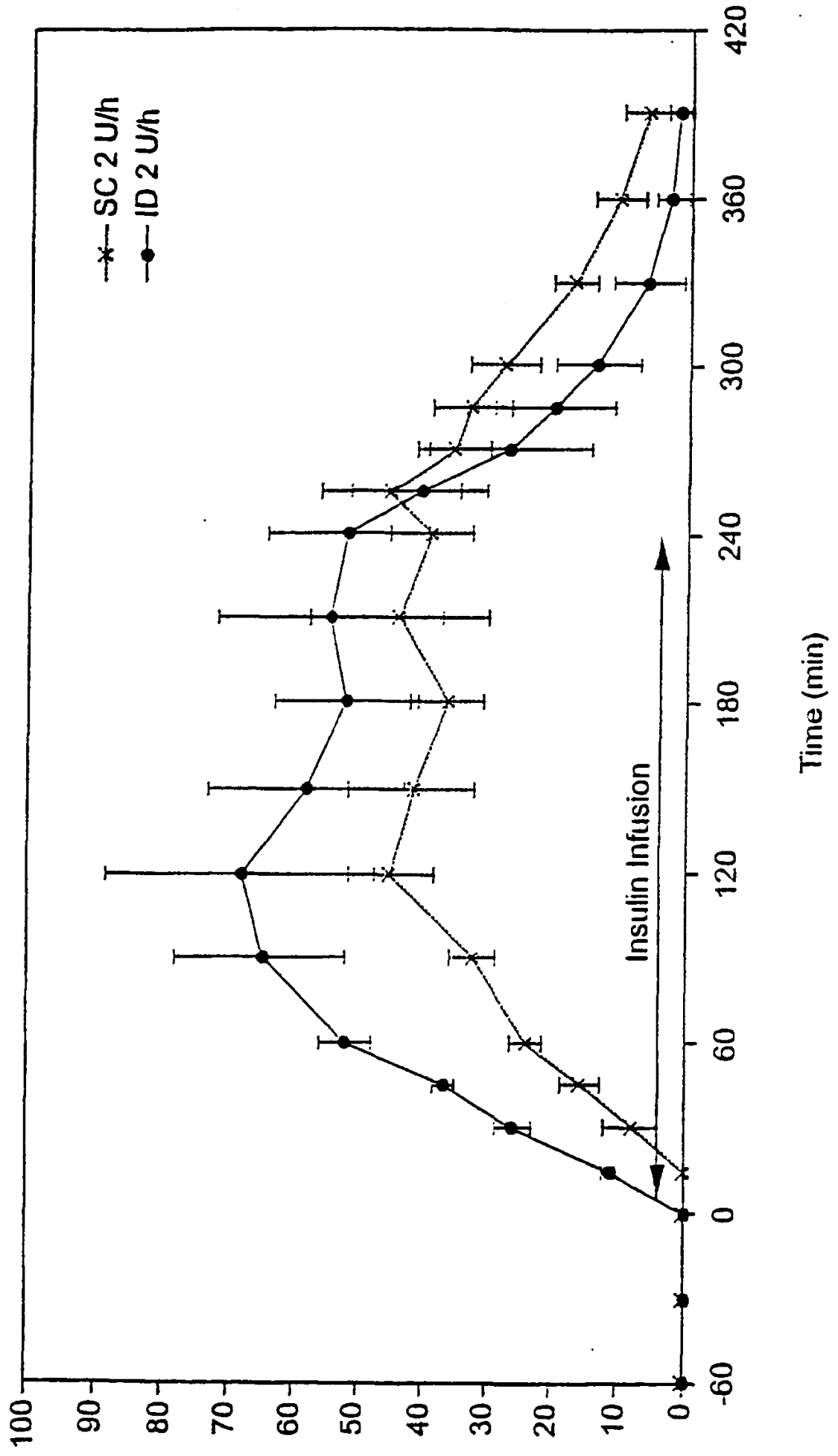
8
Time (hours)

FIG. 4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ID 2 U/h
Insulin Infusion
Plasma Insulin (uIU/mL)
Time (min)
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70
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90
100
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60
120
180
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300
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/20763

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	US 3 964 482 A (GERSTEL MARTIN S ET AL) 22 June 1976 (1976-06-22) abstract	17-24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 November 2001	12/11/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/20763

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